

APPARATUS AND METHOD FOR MANUFACTURING MOULDED PRODUCTS

5 The invention relates to the manufacture of moulded
products, especially tablets and powder plugs for
encapsulation, for example, produced by the compression of
particulate material, for example, powders and granules.
The term "tablet", as used herein, includes pharmaceutical
10 tablets, vitamin and/or mineral tablets and confectionery.

Pharmaceutical tablets are usually prepared by the instantaneous compression of a powder, comprising the active ingredient and an excipient, between two punches in a die. The force for compression may be supplied by either the upper punch or by both the upper and lower punches, but in neither case does all of the applied force go into compressing the powder. Although some of the force is lost in heat and sound energy a major proportion is absorbed in overcoming die wall friction. These frictional forces are sometimes so great as to prevent tablet compression altogether, and in other cases the appearance of the tablets is unacceptable; for example the tablets may be chipped, capped or laminated rendering them unsuitable for further processing.

25 In order to obviate these problems it has been usual to incorporate a lubricant, especially magnesium stearate, in the powder or granules to be tabletted or moulded.

The use of magnesium stearate lubricant has, however, given rise to a number of problems, especially in the production of pharmaceutical tablets but also for other moulded products. The principal problems are

(a) it is an extremely hydrophobic powder which can adversely affect the bioavailability of drugs and is

undesirable in soluble tablets where it produces a surface film or scum on the glass of water in which the tablet is dissolved; and

- (b) the mixing time used to incorporate the magnesium stearate in the other ingredients of the tablet formulation is critical and can influence the physico-mechanical properties of the tablets produced.

Similar problems arise in the use of other lubricant materials.

- 10 In EP 0 225 803A, there is described an improved method of making moulded products such as tablets in which the effectiveness of the added lubricant is increased by means of electrostatically charging the lubricant and introducing it into the die in advance of the material to be moulded. In that manner, it may be possible to reduce the amount of lubricant material remaining in the resulting product, but it would be desirable to reduce still further the need for lubrication.

- 20 The punches and the dies of the moulding devices previously used for the manufacture of tablets are typically formed of steel. Because of the repeated reciprocation of the punches within their associated die, on the repeated compression of the material to be formed into tablets, both the punches and the die are subjected to a high degree of wear. In practice, a hardened steel has been used for the manufacture of the punches and dies. Even with such hardened steel materials, lubricated in the manner described above, the severe abrasion to which the parts are subjected in use results in wear, and may result in the shedding of small amounts of the metal into the substrate. The presence of that material in the resulting tablets, albeit being substantially non-toxic in the amounts obtaining in normal practice, is undesirable.

In order to minimise the occurrence of undesired wear in the use of such parts it has been usual to make the moulding surfaces of the parts relatively simple in configuration, for example, flat, or gently curved into a concave surface.

Powder plugs for incorporation into hard gelatin capsules may be made using a dosator. Dosators of the type conventionally used to make such plugs include a cylindrical casing ("dosage tube"), defining a cylindrical bore in which is located a piston ("dosage punch"). In use, the dosage tube is lowered downwardly into a hopper containing the powder to be compressed by means of relative vertical movement of the hopper and the dosage tube the dosage punch lightly compressing the powder to form a plug which remains within a lower portion of the dosage tube when that is lifted out of the surrounding powder, and can subsequently be ejected from the tube into an open capsule body by operation of the dosage punch. Whilst the forces to which the dosator is subjected are less than in the case of the working parts of tableting machines, there can be a tendency for friction and wear to occur, especially in the processing of compositions including relatively abrasive components. It is therefore customary to include conventional lubricants, such as magnesium stearate, in the formulations used, as well as other conventional additives such as flow aids.

The invention provides a part for use in a moulding apparatus, the part comprising a shaped member comprising zirconia.

Zirconia has been found to have particularly suitable properties for use in those parts in tableting machines that will be in contact with the material to be moulded. It is a very hard material, and thus resistant to abrasion.

The use of zirconia offers significant advantages in terms of wear resistance, and thus in terms of the length of the useful life of the parts. Zirconia is substantially non-toxic when ingested in small quantities so that, should any
5 abraded material from the shaped part enter the moulded tablet, that will not detrimentally affect the acceptability of the tablets, whether for pharmaceutical or other use.

A further advantage is that, because of its relative
10 hydrophilicity, zirconia offers a low coefficient of friction in the context of moulding. It is thought that this unexpectedly low coefficient of friction is accounted for by the fact that the surface of the zirconia attracts a monolayer of water molecules, which acts as a lubricant
15 during the manufacturing process. The present inventors have thus found that zirconia has an advantageous spectrum of properties which, in combination, make it especially effective in the moulding of tablets.

It is believed that the use of zirconia in the devices
20 for use in the manufacture of lightly compressed plugs for incorporation in capsules will offer similar advantages.

Advantageously, the part is a punch. The shaped member may constitute the whole punch. If preferred, however, the shaped member may constitute a component of
25 the punch, the punch comprising at least one further component, which may be of zirconia or of any other suitable material, for example steel. In that case, it will be appreciated that at least that portion of the surface of the punch that in use contacts the material to
30 be moulded will be constituted by the shaped member comprising zirconia.

The shaped member comprising zirconia may include a surface having at least one protrusion arranged to form, in

use, a corresponding recess or recesses in an article moulded using the part. The shaped member comprising zirconia may include a surface having at least one recessed region arranged to form, in use, a corresponding embossed region or regions on an article moulded using the part. Said at least one protrusion or at least one recessed region may be in the form of one or more letters of the alphabet. A punch according to the invention enables there to be formed embossed region(s) and/or recess(es) on the surface of the moulded article, for example, tablet, in reproducible fashion, even after many thousands of moulding cycles. The shaped member comprising zirconia may be configured and dimensioned to impart to an article to be moulded a feature or features of configuration that is or are substantially invisible to the naked eye. The shaped member comprising zirconia may be configured to impart to an article to be moulded a feature of configuration which is suitable for distinguishing the article from a counterfeited article.

In consequence, it is possible by means of imparting to the punch or punches to be used in the manufacture of articles a unique pattern, which may for example be in the form of a letter or letters of the alphabet identifying the manufacturer or constituting a trade mark associated with the articles, in the form of braille letters enabling blind consumers reliably to distinguish the articles from other similar articles, or in the form of a distinctively shaped design, such as a logo. Incorporation of such a unique pattern may have a number of advantages from the point of view of distinguishing the articles from other articles of similar type, but may especially be useful in enabling genuine articles to be distinguished from counterfeit articles. It is a particular advantage of the punches of

The shaped member may advantageously consist essentially of zirconia. For example, the shaped member advantageously contains at least 90%, preferably 95%, and more preferably 97%, by weight, based on the total weight of the member, of zirconia. One or more suitable compounds selected from yttria and other metal oxides may advantageously be present in small amounts, for example, up to 10%, preferably up to 5% by weight based on the total weight of the member to stabilise the lattice structure of the zirconia. If preferred, the shaped member may be of zirconia and another suitable material. For example, it may be of a blend comprising zirconia and alumina. In that case, the shaped member may comprise, for example, from 5 to 20% by weight zirconia in admixture with alumina.

The invention further provides a moulding apparatus comprising at least one punch comprising a shaped member comprising zirconia as defined above and/or at least one die comprising a formed member comprising zirconia as defined above. Advantageously, the moulding apparatus comprises at least one pair of punches and a die which are each so configured that they cooperate to form, in use, a moulded article having a plurality of edges and corners.

Tabletting machines comprising punches and dies consisting wholly or in part of zirconia as described above offer particular advantages in the manufacture of embossed tablets. The use of zirconia parts of suitable configuration will also facilitate the manufacture of tablets of given desired configurations, and may be especially advantageous in the manufacture of tablets having more than the usual number of edges or of unusual shapes, enabling a wider range of tablet shapes to be generated satisfactorily. In practice, it will be preferable for the tabletting machine to incorporate a pair

of punches and a die which together cooperate to form the tablet, and at least those portions of the opposed punches that in use contact the tablet will comprise zirconia.

In a preferred embodiment of the invention described
5 below the tabletting machine is a rotary press. In such presses, a multiplicity of pairs of punches operate sequentially and the pressing cycle is initiated by a cam mechanism which acts on a portion of each punch (that portion being referred to below as a "cam follower"). It
10 may be advantageous for the cam follower to comprise zirconia, rendering the cam follower more resistant to wear. It may also be advantageous for the cam to comprise zirconia.

The moulding apparatus may be suitable for use in the
15 manufacture of powder plugs for encapsulation in gelatin capsules, for example, it may be a device of the type known as a dosator. In that case, the shaped member advantageously constitutes the dosage tube of the dosator. It may be preferred, however, for merely the tip of the
20 dosage tube, in particular the portion that in normal use comes into contact with the composition to be compressed, to comprise zirconia.

Moreover, the invention provides a method of making a moulded article, which is administrable to a human or
25 animal, especially an ingestible article, comprising introducing a zirconium-containing compound into a mould with the material to be moulded. The lubricating properties of the zirconium-containing compound may render the use of other lubricating materials unnecessary
30 (although the presence of such other lubricants is not excluded, if desired). The use of zirconium-containing compounds, especially zirconia, as a lubricating ingredient offers advantages over conventional lubricants, such as

magnesium stearate, in particular in that it has a lesser effect on the solubility characteristics of the other ingredients of the moulded article.

It will be appreciated that the zirconium-containing compound should be a physiologically tolerable compound. The zirconium-containing compound may be introduced into the mould in admixture with the material to be moulded. As well, or instead, the zirconium-containing compound may be introduced into the mould in advance of the material to be moulded. The zirconium-containing compound may be zirconia, but is preferably zirconium hydroxide or a physiologically tolerable zirconium salt. Zirconium-containing compounds for use in the manufacture of moulded articles according to the invention will advantageously be in the form of powders, of which the maximum particle size is not more than 10 μ m. Whilst the use of material of greater particle size is also possible, it may then be necessary to increase the quantity of the zirconia present to achieve a corresponding degree of lubricity. Zirconia powder for use in the manufacture of the moulded articles may be made by calcination of finely divided zirconia.

Advantageously, the moulded article is a tablet. Preferably, the moulded article is a pharmaceutical tablet. The invention further includes a tablet comprising a zirconium-containing compound.

The moulded article may be a powder plug for encapsulation in a gelatin capsule. The invention further provides a hard gelatin capsule including an encapsulated composition comprising a zirconium-containing compound.

The zirconium-containing compound to be incorporated in the moulded article may be in the form of a gel or of small particle size particulates, which may be obtained for example by means of spray drying, lyophilisation or size

reduction from larger particles. The zirconium-containing compound may be incorporated in mixtures of drugs or drug formulations in amounts of, for example 0.05% to 20%, and preferably not more than 10%, more preferably not more than 5%, by weight based on the total weight of the combined components. Amounts of zirconium-containing compound exceeding 20% by weight are not excluded, although it is believed that no further significant improvement in lubrication will be obtained if greater amounts are used.

The presence of the zirconium-containing compound may improve the flow, adherence and lubrication properties of such mixtures. The zirconium-containing compounds may be used in combination with, or as alternatives to, materials currently used for flow improvement, adherence or lubrication.

By way of example, a rotary press tabletting machine including a multiplicity of dies and punches embodying the invention will now be described with reference to the accompanying drawings, of which:

Fig. 1 is a schematic developed view of a rotary press;

Fig. 2 is a vertical section through a punch having a zirconia tip;

Fig. 3 is a vertical section through a die having a zirconia lining;

Fig. 4 is a graph in which the ejection forces in a steel die and a zirconia die are compared in respect of micro-crystalline cellulose tablets;

Fig. 5 is a graph corresponding to Fig. 4 in respect of silicified micro-crystalline cellulose tablets;

Fig. 6 is a graph corresponding to Fig. 4 in respect of lactose tablets;

Figs. 7a to 7e are graphs of ejection force against ejection time for a microcrystalline cellulose tablet previously compacted at compaction speed 100mm per second and at a compaction force of 2kN(Fig. 7a), 4kN (Fig. 7b), 8kN (Fig. 7c), 12kN (Fig. 7d), and 16kN (Fig. 7e);

The rotary press shown in the drawing is entirely conventional, except for the punches and dies which, as described further below, are in accordance with the invention. The rotary press may, for example, be a rotary press of the Type RB3 (trade mark) manufactured by Manesty Machines Ltd. The press has a circular die table 1 mounted for rotation about its central axis. A plurality of dies 2 are located in the table 1. Above and aligned with each die 2 is an associated upper punch 3 mounted for sliding movement into and away from the die in an upper punch holder 4 which, in turn, is arranged for rotation with the die table 1. Similarly, below and aligned with each die 2 is an associated lower punch 5 mounted for sliding movement into and away from the die in a lower punch holder 6 which, in turn, is arranged for rotation with the die table 1. Each of the upper punches 3 has a cam follower 7 at its upper end and similarly each of the lower punches 5 has a cam follower 8 at its lower end. The cam followers 7 rest on a stationary fixed upper cam track 9 while the cam followers 8 rest on a stationary fixed lower cam track 10. The die table 1, dies 2, punches 3, 5 and punch holders 4, 6 are made of metal.

The lower cam track 10 is interrupted at one position by a ramp 11 the height of which can be screw-adjusted and at another position by the head of an ejection knob 12 which is also screw-adjustable.

A pair of compression rolls 13 are also associated with the upper and lower cam tracks 10 and 11.

The press has a main hopper 14 for feeding the powder or granules to be tabletted. In a conventional arrangement this powder would include lubricant particles but in the described apparatus that may not be necessary (although it is not excluded). The hopper 14 has an outlet leading to a stationary feed frame or a force feeder with moving paddles 15 immediately about the die table 1. The base of the frame 15 lies immediately adjacent to the top of the die table 1 and has apertures which allow powder or granules to pass from the compartment into the dies 2.

A stationary blade 16 is provided for scraping excess powder or granules away from the dies 2.

In operation of the press the die table 1 and the upper and lower punch holders 4, 6, which together form a common unit, are rotated in the direction from left to right as seen in the drawing, which is a developed view, the right hand edge of the drawing joins up with the left hand edge.

A given die 2, having an associated lower punch 5 and upper punch 3, moves to a position underneath the feed frame 15 where the die is filled with powder. As the die moves to that position the cam follower 8 is caused to move down by the downwardly sloping cam track 10 so that the lower punch 5 only just projects into the die and the die is therefore almost entirely filled with powder. The cam follower 8 subsequently reaches the ramp 11 and is driven upwardly thereby expelling powder. The cam follower 8 subsequently reaches the ramp 11 and is driven upwardly thereby expelling powder from the die. While the cam follower 8 is on the top of the ramp 11 the blade 16 scrapes away excess powder from above the die. Thereafter the lower punch 5 is lowered as the cam follower 8 returns to the cam track 10 and the upper punch 3 drops as the cam

5 follower 7 slides down the inclined upper cam track 9. The upper and lower punches 3, 5 are finally forced together by the compression rollers 13 compressing the powder in the die 2 and forming a tablet. Then the upper punch 3 is raised and the lower punch 5 also raised until the tablet is swept away into a collector (not shown) by a wall. The cycle of operation is then repeated.

10 With reference to Fig. 2, a punch 3 suitable for use in the machine of Fig. 1 may have a steel body 17, to which is fixedly attached a tip 18, which is of zirconia. If desired, the end portion of the punch opposed to the tip 17 (which opposed end portion includes at least the cam follower surface 7) may also be of zirconia, although such a construction is not illustrated in Fig. 2. The punch 3
15 may, instead, be wholly of zirconia, and may then be monolithic.

20 In Fig. 3, a die 2 suitable for use in the machine may have an outer casing 19 of steel and a lining 20 of zirconia defining a cylindrical bore 21. As in the case of the punch 3 the die may, however, be wholly of zirconia and may then be monolithic. For use in a press according to Fig. 1, the punch tip diameter and the die internal diameter may each be 10 mm.

25 A die or punch or a shaped die lining or punch tip according to the invention may be of stabilised zirconia which may be manufactured from a tetragonal zirconia powder which may contain for example 3mol% yttria in solid solution, the presence of yttria contributing to the stability of the tetragonal phase. In addition to yttria
30 or instead, other additives, for example one or more other oxides, may be used to stabilise the zirconia product. The powder, including any additives, may then be pressed into shape by any suitable technique, for example, die pressing

or hydrostatic pressing or both of those techniques used sequentially. Other methods such as slip casting may be used.

The green body (that is, the shaped powder compact) may then be sintered, for example, by heating in a furnace under a controlled heating cycle to a maximum temperature between 1300°C and 1600°C, preferably in the range 1400°C to 1500°C, and maintaining this temperature for 2 to 12 hours. The temperature may then be lowered slowly to room temperature.

The shaped member so obtained may then be machined to the precise final configuration and dimensions required, to give a close fit between the cooperating punch and die, for example, using diamond grinding techniques. It is in particular desirable to ensure that sharp edges are removed by imparting in their place a small radius of curvature as the presence of sharp edges would lead to regions of stress concentration in use.

Where the punches are to have a recessed or raised region for forming a corresponding embossed or recessed region on the tablet, the desired pattern may be generated on the punch tip by any suitable method, for example, by machining the tip using suitable diamond tooling, or by appropriate modification of the method of manufacture of the tip. The pattern may be introduced during manufacture by green machining the pattern onto the tip surface to a calculated shape and size and subsequently sintering (the densification on sintering causing shrinkage of dimensions with the pattern being essentially retained), or by impressing the pattern, to a calculated shape and size, into the powder compact and sintering to full density. It will be appreciated that, in each case, when calculating the appropriate shape and size, allowance will have to be

made for the shrinkage that will occur on sintering. The patterns so produced are of relatively high definition.

In the case where a zirconia lining is provided, which in use is combined with a die casing, the liner in the form of a thin walled cylinder is, after sintering, diamond machined such that its diameter is slightly larger than the internal diameter of the outer die casing. The casing, which may be of, for example, tool steel, may be heated to expand its internal diameter and the zirconia insert may then be inserted and the casing shrink fitted onto the liner, imposing compressive stresses on the liner, both holding it in place and strengthening it. The inner diameter of the lining may then be diamond honed to give it the desired final dimensions.

Where the member is a punch tip, the tip may be held in place by any suitable means, for example, mechanical means, any suitable adhesive or metallic braze, or a suitable combination of one or more of those means. Suitable mechanical means may include the provision of cooperating means on the tip and the punch body, for example, means permitting an interlocking fit or a screw fit. Suitable adhesives are preferably organic-based adhesives. Because the stresses on the tip are mainly compressive in nature, it is in general unnecessary to take any special measures to ensure that the affixment of the tip to the remainder of the punch is of very high strength.

Fig. 4 is a graph of the ejection force required to eject from a die a compressed portion of microcrystalline cellulose powder against the compaction force previously applied to the compressed portion to be ejected. The powder did not contain any conventional lubricant additives. As indicated in Fig. 4, the upper line represents measurements made using as the die a steel die,

and the lower line represents measurements made using as the die a zirconia die according to the invention. In each case the lower opening of the die is closed by a lower punch, arranged to be stationary, and the material is compacted by an upper, vertically movable punch. The upper and lower punches are, in each case, of the same material as the die, that is, of steel or zirconia, respectively. As is apparent from Fig. 4, the ejection force required in the case of the steel die is significantly greater than in the case of the zirconia die. The measurements were obtained by compressing a portion of the microcrystalline cellulose in the die by advancing the upper punch downwardly at a speed of 10 mm per minute until the desired compaction force is reached and thereafter inverting the die together with the compressed portion contained therein and advancing the punch downwardly onto the compressed portion and determining the ejection force required to eject it. The compaction force and ejection force were measured using an Instron tensile testing machine, having a load cell arranged to measure the force transmitted through the punch. The compaction force and the ejection force are the peak force, determined in each case by the load cell, during compaction and ejection, respectively.

Fig. 5 is a corresponding graph of the ejection force against compaction force for compressed portions of silicified microcrystalline cellulose, without added lubricant and Fig. 6 is an analogous graph for compressed portions of lactose containing 1% by weight magnesium stearate as added lubricant. In each case, the upper line represents measurements made using as the die a steel die, and the lower line represents measurements made using as the die a zirconia die according to the invention, and the relative positions of the lines show that the ejection

force required in the case of the steel die is significantly greater than in the case of the zirconia die.

Many pharmaceutical tablets contain as a significant component one or more diluents selected from

5 microcrystalline cellulose, silicified microcrystalline cellulose and lactose, and Figs. 4 to 6 demonstrate the benefit of the advantageous frictional behaviour of zirconia in the manufacture of tablets. In the presence of added lubricant, the superior performance of zirconia will

10 still be observable, at a given lubricant content.

Tests carried out using a compaction simulator (consisting either of a zirconia die and a pair of opposed zirconia punches according to the invention or of a steel die with a pair of steel punches) showed that the punches

15 and die of the invention performed well without any detectable deterioration at high speeds, and at loads of 16 kN and greater. Figs. 7a to 7e are graphs showing the relationship between ejection force and ejection time for a microcrystalline cellulose tablet, incorporating 0.5 wt %

20 magnesium stearate as added lubricant, the tablet having previously been compacted in the compaction simulator. Compaction of the tablets was accomplished using a sawtooth profile compaction cycle, with a punch tip velocity of 100mm per second, at a selected compaction force. (Punch

25 tip velocity in the compaction simulator may be determined using a linear variable displacement transducer.)

Fig. 7a relates to tablets previously compacted at compaction force 2kN, Fig. 7b to tablets compacted at 4kN, Fig. 7c to tablets compacted at 8kN, Fig. 7d to tablets

30 compacted at 12kN and Fig. 7e to tablets compacted at 16kN. In each of Figs. 7a to 7d, each curve represents the averaged results for at least five tablets. The area under each curve represents the work needed to overcome die wall

friction during ejection, and it will be seen that, in each of Figs. 7a to 7e, the area under the curve representing tablets ejected from zirconia tools is less than that under the curve representing tablets ejected from steel tools, indicating a significant reduction in ejection forces.

Microcrystalline cellulose used in the above methods was of the type known as EMCOCEL 90M, obtainable from Mendell UK Ltd. Where magnesium stearate was used as an additive, it was incorporated in the powder before compaction by mixing for five minutes in a Turbula mixer at slow speed. All powders were stored before use for at least one day in the desiccator at room temperature and relative humidity 44%. Where used, the compaction simulator was fitted with 10mm diameter flat-faced round F-tooling manufactured from zirconia or steel. The compaction speed used was 100mm/sec corresponding to the main compaction time of 0.345 seconds. A single saw-tooth control profile was chosen to provide the main compaction pressures. The die was filled manually, sufficient powder being used to produce a tablet thickness of about 2.5mm at zero porosity. During tableting, relative humidity was within the range of 35 to 45% and temperature within the range 20 to 25°C.

The punches and dies used in the Instron tester and in the compaction simulator were all of type suitable for use in the press of Fig. 1.

Shaped members comprising zirconia according to the invention have also been found to exhibit excellent wear resistance, and have high strength, high fracture toughness and high hardness. Other properties of zirconia which it is thought may contribute to its excellent performance in the manufacture of tablets are its anti-static properties, non-magnetic nature, low thermal conductivity and good

corrosion resistance. A consequence of the advantageous combination of properties is that the amounts of material shed into the tablet formulation are likely to be considerably reduced as compared with the steel parts conventionally used, and may be substantially eliminated. The tablets manufactured using zirconia members according to the invention may, moreover, be of improved strength.

It may also be advantageous to use a part comprising a shaped member comprising zirconia in a device for moulding powder plugs for subsequent encapsulation. In that case, the forces to which the part will be subjected in use will be lower than in a tableting machine. In the case of a moulding device of the type known as a dosator, it may be appropriate to use a single walled cylindrical tube of zirconia, for example of wall thickness 1mm, as the dosage tube itself or as the tip portion of the dosage tube.

The following Examples are illustrative of those methods of the invention in which a zirconium-containing compound is incorporated in a tablet composition. In the Examples, references to % are % by weight based on the total weight of the composition.

Example 1

	Ingredients	%	mg per tablet
	Frusemide EP	25.0	40.0
25	Microcrystalline		
	Cellulose USP NF	12.0	19.2
	Croscarmellose		
	Sodium USP NF	1.5	2.4
	Lactose EP	59.5	95.2
30	Zirconia powder	2.0	3.2
	Total	100.0	160.0

The zirconia, in the form of particles of diameter less than 10 μ m and obtainable by calcination of the fine oxide, are mixed with the other ingredients by tumbling for 5 minutes and the particulate mixture is introduced into a hopper of a rotary press such as that shown in Fig. 1 and pressed therein to produce 160 mg tablets without the use of conventional lubricants such as magnesium stearate. If required, determination of particle size may be carried out by any method suitable having regard to the material and particle size, for example, by low angle laser light scattering using an apparatus such as the Malvern Mastersizer X (trade mark).

Example 2

	Ingredients	%	mg per tablet
15	Allopurinol EP	55.7	300.0
	Dibasic calcium		
	Phosphate USP NF	37.2	200.0
	Sodium starch		
	Glycollate USP NF	3.8	20.5
20	Zirconia powder	3.3	17.5
	Total	100.0	538.0

The ingredients were mixed and pressed in similar manner to that described in Example 1 to produce 538 mg tablets.

Measurements using flow testing equipment (Aeroflow tester, Flo-Dex apparatus and bulk density apparatus) indicated that calcined zirconium oxide (prepared by heating to 400°C for nine hours) improved the flow properties of microcrystalline cellulose (EMCOCEL 50) when present at concentrations of 1%, 2% and 5% w/w.

There may be used instead of zirconia in the above formulations (or in any other formulation according to the

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